



## **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.**

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# Cystoisosporiasis (Formerly Isosporiasis) (Last updated September 10, 2015; last reviewed June 26, 2019)

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## Epidemiology

Isosporiasis, also known as cystoisosporiasis, occurs worldwide but predominantly in tropical and subtropical regions. Immunocompromised patients, including those who are HIV-infected, are at increased risk for chronic, debilitating illness.<sup>1-7</sup> Although *Isospora* (*Cystoisospora*) *belli* completes its life cycle in humans, the oocysts shed in the feces of infected individuals must mature (sporulate) outside the host, in the environment, to become infective. On the basis of limited data, the maturation process is completed in approximately 1 to 2 days but might occur more rapidly in some settings.<sup>2</sup> Infection results from ingestion of sporulated oocysts, such as from contaminated food or water. After ingestion, the parasite invades enterocytes in the small intestine. Ultimately, immature oocysts are produced and shed in stool.

## Clinical Manifestations

The most common manifestation is watery, non-bloody diarrhea, which may be associated with abdominal pain, cramping, anorexia, nausea, vomiting, and low-grade fever. The diarrhea can be profuse and prolonged, particularly in immunocompromised patients, resulting in severe dehydration, electrolyte abnormalities such as hypokalemia, weight loss, and malabsorption.<sup>6-12</sup> Acalculous cholecystitis/cholangiopathy<sup>2,13-15</sup> and reactive arthritis<sup>16</sup> also have been reported.

## Diagnosis

Typically, infection is diagnosed by detecting *Isospora* oocysts (dimensions, 23–36  $\mu\text{m}$  by 12–17  $\mu\text{m}$ ) in fecal specimens.<sup>2</sup> Oocysts may be shed intermittently and at low levels, even by patients with profuse diarrhea. Diagnosis can be facilitated by repeated stool examinations with sensitive methods, such as modified acid-fast techniques, on which oocysts stain bright red, and UV fluorescence microscopy, under which they autofluoresce.<sup>2,17</sup> Infection also can be diagnosed by detecting oocysts in duodenal aspirates/mucus or developmental stages of the parasite in intestinal biopsy specimens.<sup>2,10</sup> Extraintestinal infection, such as in the biliary tract, lymph nodes, spleen, and liver, has been documented in postmortem examinations of HIV-infected patients.<sup>2,18-20</sup>

## Preventing Exposure

Because *I. belli* is acquired by ingesting infected water or food, avoiding potentially contaminated food or water in isosporiasis-endemic areas may help prevent infection.

## Preventing Disease

In some settings, chemoprophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with a lower incidence or prevalence of isosporiasis.<sup>1,3,4,21</sup> In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment).<sup>1</sup> In an observational study, incidence of isosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in patients with CD4 counts <50 cells/mm<sup>3</sup>.<sup>3</sup> After adjustment for the CD4 T lymphocyte (CD4) cell count, the risk of isosporiasis was substantially lower in those receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine (unspecified regimens). In analyses of data from a Los Angeles county AIDS surveillance registry during the pre-ART era, the prevalence of isosporiasis was lower in patients with versus without a history of *Pneumocystis pneumonia*—indirect evidence of a protective effect from use of TMP-SMX for *Pneumocystis pneumonia*.<sup>4</sup> Insufficient evidence is available, however, to support a general recommendation for primary prophylaxis for isosporiasis per se, especially for U.S. travelers in isosporiasis-endemic areas.

## Treating Disease

Clinical management includes fluid and electrolyte support for dehydrated patients and nutritional supplementation for malnourished patients (**AIII**). TMP-SMX is the antimicrobial agent of choice for treatment of isosporiasis (**AI**). It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails (**AIII**).

Three studies in HIV-infected patients in Haiti have demonstrated the effectiveness of various treatment regimens of TMP-SMX.<sup>6,7,22</sup> The patients were not receiving ART, and laboratory indicators of immunodeficiency (such as CD4 cell counts) were not specified. On the basis of the initial studies,<sup>6,7</sup> the traditional treatment regimen has been a 10-day course of TMP-SMX (160/800 mg) administered orally four times daily (**AII**).<sup>23</sup> In another study, TMP-SMX (160/800 mg) administered twice daily was also effective (**BI**).<sup>22</sup> Although published experience using two daily doses of TMP-SMX (160/800 mg) is limited, one approach would be to start with this regimen but to increase the daily dose and the duration of therapy (up to 3–4 weeks)<sup>6,10</sup> if symptoms worsen or persist (**BIII**). Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Limited data suggest that therapy with pyrimethamine–sulfadiazine and pyrimethamine–sulfadoxine may be effective.<sup>2,9,10,24–26</sup> However, the combination of pyrimethamine plus sulfadoxine is not typically recommended for use in the United States (**CIII**); it has been associated with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome,<sup>27</sup> and pyrimethamine and sulfadoxine clear slowly from the body after therapy is discontinued.

Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis.<sup>3,28,29</sup> Pyrimethamine (50–75 mg/day) plus leucovorin (10–25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients (**BIII**).

The author panel has issued a statement on the availability of pyrimethamine. For more information, please visit <https://aidsinfo.nih.gov/news/1604/notice-of-availability-of-pyrimethamine>.

## Special Considerations with Regard to Starting ART

Only limited data address the utility of ART in the setting of *Isospora* and HIV co-infection.<sup>3,14,21</sup> Immune reconstitution with ART may result in fewer relapses of isosporiasis, and no cases of immune reconstitution inflammatory syndrome (IRIS) have been reported. Therefore, the potential benefits of ART likely outweigh the risks. For patients with isosporiasis who otherwise fulfill criteria for ART, TMP-SMX therapy and ART can be started simultaneously; there is no known reason to defer initiation of ART other than the potential for poor ART absorption (**AIII**).

## Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients should be monitored for clinical response and adverse events. In HIV-infected patients, TMP-SMX therapy is commonly associated with side effects, such as rash, fever, leukopenia, thrombocytopenia, and elevated transaminase levels. IRIS has not been described.

## Managing Treatment Failure

If symptoms worsen or persist despite approximately 5 to 7 days of TMP-SMX therapy, the possibilities of noncompliance, malabsorption, and concurrent infections/enteropathies should be considered; the TMP-SMX regimen (daily dose, duration, and mode of administration) also should be reevaluated. For patients with documented sulfa intolerance or in whom treatment fails, use of a potential alternative agent (typically pyrimethamine) should be considered. Ciprofloxacin is a second-line agent (**CI**). On the basis of limited data from a randomized, controlled trial in Haiti, ciprofloxacin (500 mg twice daily for 7 days) is less effective than TMP-SMX but may have modest activity against *I. belli*.<sup>22</sup>

Unsubstantiated or mixed data are available for albendazole,<sup>29-31</sup> nitazoxanide,<sup>32,33</sup> doxycycline,<sup>34</sup> the macrolides roxithromycin and spiramycin,<sup>25,35,36</sup> and the veterinary anticoccidial agent diclazuril (**CIII**).<sup>37,38</sup> Limited data suggest that drugs such as metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone are ineffective.<sup>8,25,26,28,35,37</sup> Apparent or partial responses, if noted, may be attributable to treatment of concomitant infections or to nonspecific effects.

## Preventing Recurrence

Patients with CD4 cell counts <200 cells/mm<sup>3</sup> should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX, which is also protective against *Pneumocystis jirovecii* and *Toxoplasma gondii* infections (**AI**). In studies in Haiti, approximately 50% of patients who did not receive secondary prophylaxis had symptomatic recurrences approximately 2 months after completing a course of TMP-SMX therapy, relapses rapidly responded to retreatment, and secondary prophylaxis decreased the risk of relapse.<sup>6,7,22</sup> In a randomized, placebo-controlled trial, no symptomatic recurrences were noted in patients who received maintenance therapy with thrice-weekly TMP-SMX (160/800 mg) (**AI**).<sup>7</sup> Daily TMP-SMX (160/800 mg) and thrice-weekly TMP-SMX (320/1600 mg) have been effective (**BIII**);<sup>5,10</sup> however, clinical and parasitologic relapses despite maintenance TMP-SMX therapy and ART have been reported.<sup>14</sup>

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used (**BIII**).<sup>28</sup> On the basis of limited data, ciprofloxacin (500 mg thrice weekly) is considered a second-line alternative (**CI**).<sup>22</sup>

## When To Stop Secondary Prophylaxis

The issue of discontinuing prophylaxis has not been evaluated in a clinical trial. Chemoprophylaxis probably can be safely discontinued in patients without evidence of active *I. belli* infection who have a sustained increase in the CD4 cell count to levels >200 cells/mm<sup>3</sup> for >6 months after initiation of ART (**BIII**).

## Special Considerations During Pregnancy

TMP-SMX is the agent of choice for primary treatment and secondary prophylaxis in pregnant women, as it is in persons who are not pregnant. Although first-trimester exposure to trimethoprim has been associated with a small increased risk of birth defects,<sup>39-42</sup> TMP-SMX therapy should be provided in the setting of maternal symptomatic *I. belli* infection. Because of concerns about possible teratogenicity associated with first-trimester drug exposure, clinicians may withhold secondary prophylaxis during the first trimester and treat only symptomatic infection (**CIII**). Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects.<sup>43</sup> Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities.<sup>44</sup>

## Recommendations for Treating *Isospora belli* Infection

### Treating *Isospora belli* Infection

#### General Management Considerations:

- Fluid and electrolyte support in patients with dehydration (**AIII**)
- Nutritional supplementation for malnourished patients (**AIII**)

#### Preferred Therapy for Acute Infection:

- TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days (**AII**), or
- TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days (**BI**)
- One approach is to start with TMP-SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist (**BIII**)
- IV therapy for patients with potential or documented malabsorption

#### Alternative Therapy For Acute Infection (For Patients with Sulfa Intolerance):

- Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily (**BIII**), or
- Ciprofloxacin 500 mg PO BID for 7 days (**CI**)

### Chronic Maintenance Therapy (Secondary Prophylaxis)

(In Patients with CD4 Count <200/mm<sup>3</sup>)

#### Preferred Therapy:

- TMP-SMX (160 mg/800 mg) PO 3 times weekly (**AI**)

#### Alternative Therapy:

- TMP-SMX (160 mg/800 mg) PO daily (**BIII**), or
- TMP-SMX (320 mg/1600 mg) PO 3 times weekly (**BIII**), or
- Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily (**BIII**)
- Ciprofloxacin 500 mg PO 3 times weekly (**CI**) as a second line alternative

#### Criteria for Discontinuation of Chronic Maintenance Therapy

- Sustained increase in CD4 count >200 cells/mm<sup>3</sup> for >6 months in response to ART and without evidence of active *I. belli* infection (**BIII**)

**Key to Acronyms:** ART = antiretroviral therapy; BID = twice daily; IV = intravenous; PO = orally; QID = four times a day; TMP-SMX = trimethoprim-sulfamethoxazole

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